

EDITORIAL COMMENT

Making a Silk Purse Out of a Sow's Ear*

Peter R. Kowey, MD, FACC,†‡
Gan-Xin Yan, MD, PhD†
Wynnewood and Philadelphia, Pennsylvania

Precise information regarding prolongation of cardiac repolarization by non-cardiac drugs has become a highly valued commodity. The reason for this emphasis is that we now know that chemical entities that have the propensity to prolong repolarization may, under some set of circumstances, cause a particularly malignant form of ventricular arrhythmia called Torsade de Pointes (TdP). With rare exceptions, a relationship appears to exist between the magnitude of prolongation of ventricular refractoriness and the risk of developing TdP. To this point in time, the clinical parameter that has been used to measure changes in refractoriness has been the QT interval. To some extent, its use is ironic because there has been general consensus

See page 678

among experts in the field of electrophysiology that the QT interval is a relatively poor indicator of repolarization changes (1–3). Many reasons exist for this lack of support among experts, including difficulties in making precise measurements, the effects of heart rate modulation, and intrasubject and intersubject variability. Nevertheless, as bad as it is, the QT interval remains the only clinically available parameter that can be applied practically and realistically to the large population of patients that need to be evaluated not only in clinical trials but, even more importantly, in clinical practice.

So what has been done to improve on the “sow's ear” of the QT interval to glean more precise information about ventricular repolarization? This has proven to be a sticky wicket. There have been a number of strategies, including attempts to measure interlead QT dispersion, quantification of portions of the T-wave, such as T-peak to T-end, and quantification of alternations in T-wave voltage (2,4–6). To date, none of these have satisfied our need for a reliable non-invasive measurement of abnormal repolarization. The idea that has been promulgated by regulatory agencies has been to increase the reliability of the measurement of the QT interval itself by standardizing methods and by multiplying the number of observations to reduce variability.

Another important component of this refined methodology is to “calibrate the assay” by including a positive comparator in what has been referred to as “a definitive QT study.” The inference is that the demonstration of a small increase in the QT interval with a drug that has a well-defined effect on ventricular repolarization provides a measure of assurance that the techniques of QT measurement that were used in that particular experiment were adequate to arrive at satisfactory conclusions about the innovator drug. Specifically, draft guidances have stated that positive comparators chosen should be agents that are known to consistently prolong the QT interval by approximately 5 ms or less because this is the largest change that is currently viewed as clinically not important and not likely to relate to TdP. The drug that has been used most frequently for this purpose has been oral moxifloxacin, usually given at a dose of 400 mg orally.

In this issue of the *Journal*, Beasley et al. (7) report the results of a study aimed at defining the QT-prolonging effects of oral tadalafil, an inhibitor of phosphodiesterase-5 that is indicated for the treatment of erectile dysfunction. Drugs in this particular class have been shown to have a weak effect on repolarizing currents preclinically but have not been shown to have a significant effect on the QT interval or to cause TdP. Nevertheless, excluding a QT-prolonging effect of tadalafil was an integral part of the regulatory approval of that drug, as it is for any new chemical entity. However, the major point of scientific interest in this regulatory-grade study was the use of a novel positive comparator, ibutilide. At first blush, ibutilide, given its known powerful effect on ventricular repolarization, seems to have been an odd choice for this purpose. However, on closer inspection, the use of ibutilide was conscionable and reasonable. The drug was delivered in such a way as to produce reproducibly small amounts of QT-interval prolongation and, thus, it satisfactorily validated the test procedure. The study was conducted safely, with no instances of ventricular arrhythmia or excessive QT-interval prolongation, although in some patients the infusion did have to be discontinued for safety reasons.

Although the study achieved its primary objective, there are a few caveats that are worth emphasis. First, the study that was reported here was impressive in scope. More than 34,000 electrocardiograms were collected, interpreted, analyzed, and reported and this included intensive baseline sampling. This collection represents a significant expense for one relatively small clinical study. Although it was successful, we should not be satisfied to let this kind of study become the permanent standard for assessing the risk of TdP by a new chemical entity. We need to continue to search for cheaper and easier and more precise methods that might even provide definitive information about what we really care about, which is the risk of TdP.

Second, ibutilide is a potentially harmful drug. As the authors point out, there is danger inherent in using any drug that prolongs the QT interval, and it is true that ibutilide

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the †Main Line Health Heart Center, Wynnewood, and ‡Thomas Jefferson University, Philadelphia, Pennsylvania.

offers the advantage of potentially more rapid reversibility. Nevertheless, subjects need to be fully informed of the risks of using ibutilide. Facilities for prompt resuscitation have to be in place together with the expertise to monitor the QT interval carefully so that the infusion can be stopped and magnesium administered when appropriate, as was the case in this study. It also should be remembered that the use of an intravenous medication in the study of an oral drug raises distinct problems with blinding and bias that can influence the results. Blinded interpretation of the electrocardiograms, as was performed in the current study, mitigates most but not all of this concern.

Finally, this experiment sought to identify a latent effect of tadalafil or ventricular repolarization by exposing normal individuals to supratherapeutic doses of the drug. This methodology has become accepted on the basis of sound pharmacokinetic and pharmacodynamic principals. However, whether these results will truly predict TdP in the real target population that comprises patients with heart disease, including some with repolarization variants and those with subclinical gene mutation or ion channel polymorphism (3,8,9), is yet to be proven conclusively.

Beasley et al. (7) are to be congratulated for attempting to improve on a methodology that has been put into place, endorsed by regulators, and embraced by industry for learning about the safety of non-cardiac drugs. However, for all of the science and logic, QT-interval prolongation is a poor surrogate for a lethal arrhythmia that happens rarely and is catastrophic. It can be argued that any drug that prolongs the QT interval to any extent may under some circumstances cause TdP in someone, somewhere, sometime. Clearly, the challenge is to identify patients at risk in a more precise way and to couple that kind of risk assess-

ment with a more precise quantification of the proarrhythmic potential of drugs, especially when their indication is a malady that itself does not threaten life. Trying to convert the “sow’s ear” of QT-interval measurement into a “silk purse” of risk stratification is unlikely to be the final solution, but for now it is all that we can do.

Reprint requests and correspondence: Dr. Peter R. Kowey, Suite 558, Medical Office Building East, 100 Lancaster Avenue, Wynewood, Pennsylvania 19096. E-mail: koweypr@mlhheart.org.

REFERENCES

1. Hondeghem LM, Carlsson L, Duker G. Instability and triangulation of the action potential predict serious proarrhythmia, but action potential duration prolongation is antiarrhythmic. *Circulation* 2001;103:2004–13.
2. Antzelevitch C. Arrhythmogenic mechanisms of QT prolonging drugs: is QT prolongation really the problem? *J Electrocardiol* 2004;37 Suppl:15–24.
3. Fenichel RR, Malik M, Antzelevitch C, et al. Drug-induced torsades de pointes and implications for drug development. *J Cardiovasc Electrophysiol* 2004;15:475–95.
4. Mathis AS, Gandhi AJ. Serum quinidine concentrations and effect on QT dispersion and interval. *Ann Pharmacother* 2002;36:1156–61.
5. Shah RR. Drug-induced QT dispersion: does it predict the risk of torsade de pointes? *J Electrocardiol* 2005;38:10–8.
6. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. *Circulation* 1998;98:1928–36.
7. Beasley CM Jr., Mitchell MI, Dmitrienko AA, et al. The combined use of ibutilide as an active control with intensive electrocardiographic sampling and signal averaging as a sensitive method to assess the effects of tadalafil on the human QT interval. *J Am Coll Cardiol* 2005;46: 678–87.
8. Splawski I, Timothy KW, Tateyama M, et al. Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia. *Science* 2002;297:1333–6.
9. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004;350:1013–22.